



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US91/04181 (22) International Filing Date: 12 June 1991 (12.06.91) (30) Priority data: 538,375 14 June 1990 (14.06.90) US (60) Parent Application or Grant (63) Related by Continuation US 538,375 (CIP) Filed on 14 June 1990 (14.06.90) (71) Applicant (for all designated States except US): APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. [NL/ NL]; John B. Gorsiraweg 6, Curaçao (AN).		(72) Inventor; and (75) Inventor/Applicant (for US only) : HODGEN, Gary, D. [US/US]; 619 Mowbray Arch, Norfolk, VA 23507 (US). (74) Agent: WILLIAMS, Stephan, P.; Ares-Serono Inc., Ex- change Place, 37th Floor, Boston, MA 02109 (US). (81) Designated States: AT (European patent), AU, BE (Euro- pean patent), CA, CH (European patent), DE (Euro- pean patent), DK (European patent), ES (European pa- tent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (Euro- pean patent), NL (European patent), SE (European pa- tent), US. Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: COMBINED TREATMENT WITH GnRH ANTAGONIST AND GnRH TO CONTROL GONADOTROPIN LE- VELS IN MAMMALS		
(57) Abstract <p>The present invention relates to a method of controlling gonadotropin levels in mammals which comprises administering a gonadotropin releasing hormone (GnRH) antagonist in an amount and frequency effective to substantially suppress endogenous gonadotropin levels in said mammal and administering gonadotropin releasing hormone (GnRH) in an amount and frequency effective to induce secretion of gonadotropins to maintain a desired level in said mammal. This method is especially useful for treating mammals, particularly women, who suffer from polycystic ovarian disease or hyperandrogenism, or who otherwise have abnormally high levels of luteinizing hormone which it is desired to reduce to approximately normal levels. The method of this invention is particularly advantageous for inducing ovulation in mammals, particularly women, that have the above-mentioned problems. The preferred GnRH antagonists for use in the present invention include Antide and its analogs, which exhibit long term gonadotropin suppression.</p>		

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Combined Treatment with GnRH Antagonist and GnRH
to Control Gonadotropin Levels in Mammals

Background of the Invention

A common problem encountered when treating female
5 infertility is abnormal hormone levels, particularly,
abnormally high luteinizing hormone (LH) and/or androgen
levels, and often low follicle stimulating hormone (FSH)
levels. This is especially true with patients suffering from
polycystic ovarian disease (PCOD).

10 To induce ovulation and achieve a successful pregnancy in
PCOD patients various treatments have been attempted.
Excellent results have been obtained by administering
essentially pure FSH, which has been found to correct the
LH:FSH imbalance (METRODIN-The Gonadotropins in the Polycystic
15 Ovarian Disease, product brochure of The Ares-Serono Group,
1990.). It has also been suggested to administer a GnRH
agonist (Hoe 766) to suppress endogenous gonadotropin (FSH/LH)
secretion by a down-regulation mechanism and, while maintaining
such suppression, administer a conventional gonadotropin
20 treatment regimen to induce ovulation. (Coutts,
Excerpta-Medica Int'l Congress Series 652:608, 1984). While
not directed to treating PCOD, US 4,845,077 suggests that the
individual variability in response to gonadotropin therapy can
be eliminated by conjointly administering a GnRH antagonist with
25 the gonadotropin treatment.

A new generation of highly active GnRH antagonists are
disclosed in WO 89/01944. While a large number of active
decapeptides are disclosed in this publication, one of them has
been tested more extensively than the others. This decapeptide
30 has been named Antide and is represented by the formula
$$\text{N-Ac-D-2-Nal}^1\text{-DpClPhe}^2\text{-D-3-Pal}^3\text{-Ser}^4\text{-NicLys}^5\text{-D-NicLys}^6\text{-Leu}^7\text{-}$$
$$\text{ILys}^8\text{-Pro}^9\text{-D-Ala}^{10}\text{-NH}_2.$$
Antide has been shown to provide
profound long-term inhibition of tonic gonadotropin (FSH/LH)
levels in ovariectomized monkeys, the duration of such
35 inhibition being dose dependent (Leal et al, J. Clin.

Endocrinol. Metab. 67:1325, 1988). More recently, it was discovered that ovariectomized monkeys treated with Antide would respond to a large i.v. bolus of gonadotropin releasing hormone (GnRH) by showing a transient increase in gonadotropin levels which subsequently falls back to the inhibited state (Leal et al, Contraception 40:623, 1989).

Summary of The Invention

The present invention relates to a method of controlling gonadotropin levels in mammals which comprises administering a gonadotropin releasing hormone (GnRH) antagonist in an amount and frequency effective to substantially suppress endogenous gonadotropin levels in said mammal and administering gonadotropin releasing hormone (GnRH) in an amount and frequency effective to induce secretion of gonadotropins to maintain a desired level in said mammal. This method is especially useful for treating mammals, particularly women, who suffer from polycystic ovarian disease or hyperandrogenism, or who otherwise have abnormally high levels of luteinizing hormone which it is desired to reduce to approximately normal levels. The method of this invention is particularly advantageous for inducing ovulation in mammals, particularly women, that have the above-mentioned problems. The preferred GnRH antagonists for use in the present invention include Antide and its analogs, which exhibit long term gonadotropin suppression.

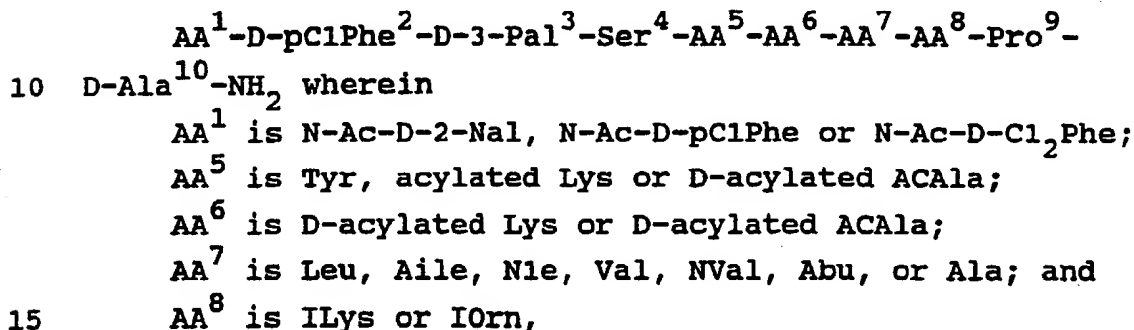
Description of the Drawings

Fig. 1 is a graph which illustrates LH and FSH response levels in ovariectomized cynomolgus monkeys treated with Antide, followed by pulsatile GnRH replacement therapy in a 7 day on, 7 day off regimen.

Description of The Preferred Embodiments

In practicing the treatment method of the present invention, it is preferred to utilize a GnRH antagonist which exhibits a long-term inhibition of gonadotropin secretion.

- 5 Particularly advantageous are the GnRH antagonists of the type disclosed in WO 89/01944, the disclosure of which is incorporated herein by reference. These GnRH antagonists include decapeptides which have the formula:



as well as structural analogs and derivatives thereof which have essentially the same activity. Such analogs and derivatives include, for example, those peptides wherein one or more amino acids have been modified, such as by substituting a
 20 different amino acid, and/or adding a substituent, such as alkyl, where such modification does not destroy the essential properties of the peptide.

Of the decapeptides which are embraced by the above mentioned formula, especially preferred are those wherein

- 25
$$\text{AA}^1 \text{ is N-Ac-D-2-Nal}$$

$$\text{AA}^2 \text{ is NicLys, PicLys, MNicLys, MPicLys, INicLys, DMGLys, or PzCLys; and}$$

$$\text{AA}^6 \text{ is D-NicLys, D-PicLys, D-MNicLys, D-MPicLys, D-INicLys, D-BzLys, D-PzCLys, D-PzACAla, D-NACAla, or D-PACAla.}$$

- 30 The most preferred GnRH antagonist is Antide, which is represented by the formula $\text{N-Ac-D-2-Nal}^1\text{-D-pClPhe}^2\text{-D-3-Pal}^3\text{-Ser}^4\text{-NicLys}^5\text{-D-NicLys}^6\text{-Leu}^7\text{-ILys}^8\text{-Pro}^9\text{-D-Ala}^{10}\text{-NH}_2$. Of course, other known GnRH antagonists may also be utilized, including, for example, $(\text{N-Ac-D-2-Nal}^1, \text{D-pClPhe}^2, \text{D-3-Pal}^3, \text{Arg}^5, \text{D-Glu}^6(\text{AA}), \text{D-Ala}^{10})\text{-GnRH}$ and $(\text{Ac-pClPhe}^1, \text{pClOPhe}^2, \text{D-Trp}^3, \text{D-Arg}^6, \text{D-Ala}^{10})\text{-GnRH}$.
- 35

In the above formulations, the following abbreviations apply:

	Ac	-	acetyl
	Abu	-	aminobutyric acid
	ACAla	-	aminocyclohexylalanine
5	Aile	-	alloisoleucine
	Ala	-	alanine
	BzLys	-	N ^E -benzoyllysine
	Cl ₂ Phe	-	3,4-dichlorophenylalanine
	DMGLys	-	N ^E -(N,N-dimethylglycyl) lysine
10	Ilys	-	N ^E -isopropyllysine
	INicLys	-	N ^E -isonicotinoyllysine
	IOrn	-	N ^E -isopropylornithine
	Leu	-	leucine
	Lys	-	lysine
15	MNicLys	-	N ^E -(6-methylnicotinoyl) lysine
	MPicLys	-	N ^E -(6-methylpicolinoyl) lysine
	NACAla	-	3(4-nicotinoylaminocyclohexyl) alanine
	2-Nal	-	3-(2-naphthyl) alanine
20	NicLys	-	N ^E -nicotinoyllysine
	Nle	-	norleucine, 2-aminohexanoic acid
	Nval	-	norvaline, 2-aminopentanoic acid
	PACAla	-	picolinoyl ACAla
	3-Pal	-	3-(3-pyridyl) alanine
25	pClPhe	-	3-(4-chloro) phenylalanine
	PicLys	-	N ^E -picolinoyllysine
	Pro	-	proline
	PzACAla	-	3(4-pyrazinylcarbonylamino- cyclohexyl) alanine
30	PzcLys	-	N ^E -pyrazinylcarbonyllysine
	Ser	-	Serine
	Tyr	-	tyrosine

In practicing the treatment method of the present invention the GnRH antagonist should be administered in an amount and frequency effective to substantially suppress endogenous gonadotropin levels during the treatment period. These parameters can be readily determined by the skilled

practitioner and must obviously be adjusted to reflect the activity of the particular antagonist utilized and the needs of the particular patient being treated so as to optimize the results to be obtained.

5 Generally speaking, antagonists such as Antide are administered in amounts between about 0.001 and 10 mg/kg body weight per day, preferably about 0.1 to 3 mg/kg/day. It may be administered at the higher range of dose levels over a period of about one to six days to achieve a long term
10 gonadotropin suppression lasting about four to eight weeks, at which point it can be readministered. Alternatively, it may be administered at the lower range of dose levels when it is administered more frequently such as daily, every other day, or weekly. It is preferred to administer the antagonist at
15 regular intervals during the treatment period to maintain inhibition of gonadotropin secretion. This may be daily, every other day, weekly, biweekly or monthly depending on the dose and formulation. When the antagonist is administered over an initial loading period of several days, it is
20 preferred to administer it once per day, or as a depot implant lasting several days per treatment. Of course, it is also possible, and may be desirable in some instances, to administer the antagonist in slow release form.

 Upon administration of an effective amount of GnRH
25 antagonist to suppress endogenous gonadotropin levels, gonadotropin releasing hormone (GnRH) is administered in an amount and frequency effective to induce secretion of gonadotropins to maintain a desired level. This desired level of gonadotropin secretion may be adjusted so as to induce
30 ovulation if that is the intended goal.

 The GnRH administration may be commenced after the first day of the GnRH antagonist administration, and preferably after completion of the GnRH antagonist administration where such administration comprises a high loading dose of
35 antagonist administered over a short (1-6 day) period. In certain instances it may be desirable or preferred to commence GnRH administration during the period of antagonist

administration (e.g. where the antagonist is administered throughout the treatment period) and, in fact, administration of both agents can commence at the same time and continue throughout the treatment period.

5 The amount of GnRH to be administered and the frequency of administration will obviously depend on the needs and condition of the patient being treated and the gonadotropin levels which are desired to be maintained in that patient. Typically, GnRH replacement therapy will continue daily during
10 the treatment period, preferably in an episodic or pulsatile manner, generally at levels of about 5 to 10 μ g/pulse every 60 to 120 minutes, preferably through an infusion pump. Where it is desired to induce ovulation in humans, the GnRH replacement therapy will ordinarily continue for about sixteen days,
15 preferably followed by human chorionic gonadotropin.

 The treatment method of the present invention is useful for controlling gonadotropin levels in mammals, particularly women, so that they can be maintained at a desired level, particularly levels within the normal range, and most
20 particularly levels which will induce ovulation. This method is especially suitable for treating mammals, particularly women, with polycystic ovarian disease, hyperandrogenism, or abnormally high levels of luteinizing hormone.

 For use in practicing the above-described method, this
25 invention also contemplates a treatment kit which comprises a GnRH antagonist, as previously described, in a dosage form and quantity suitable for administering an amount and frequency effective to substantially suppress endogenous gonadotropin levels in the mammal to be treated, and GnRH in a dosage form
30 and quantity suitable for administering an amount and frequency effective to induce secretion of gonadotropins in the mammal to be treated so as to maintain a desired gonadotropin level therein.

 The GnRH antagonist may be formulated with any suitable
35 pharmaceutically acceptable carrier and may be administered by

any of a variety of routes including parenterally (including subcutaneous, intramuscular or intravenous administration), vaginally, rectally, buccally, (including sublingually), transdermally or intranasally.

5 Pharmaceutical compositions may be prepared for use for parenteral (subcutaneous, intramuscular or intravenous) administration particularly in the form of liquid solutions or suspensions; for vaginal or rectal administration particularly in semisolid forms such as creams and suppositories; for oral
10 or buccal administration particularly in the form of tablets or capsules; or for intranasal administration particularly in the form of powders, nasal drops or aerosols. Various slow release, depot implant or injectable dosage forms may also be utilized.

15 These compositions may conveniently be administered in unit dosage form and may be prepared by any of the methods well-known in the pharmaceutical art. Formulations for parenteral administration may contain as common excipients sterile water or saline, alkylene glycols such as propylene
20 glycol, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Formulations for vaginal or rectal administration, e.g. suppositories, may contain as excipients, for example, polyalkleneglycols, vaseline, cocoa butter and the like.
25 Formulations for nasal administration may be solid and contain as excipients, for example lactose or dextran, or may be aqueous or oily solutions for administration in the form of nasal drops or metered spray. For buccal administration, typical excipients include sugars, calcium stearate,
30 pregelatinated starch and the like. One or more surfactant acids or salts can be added to the solution or powder formulation. Suitable pharmaceutically acceptable surfactant salts will be those which retain the phenomenon of enhanced peptide absorption, as well as the compound's surfactant
35 characteristics and which are not deleterious to the subject or otherwise contraindicated.

Example 1

In order to demonstrate the continued long-term inhibition for endogenous gonadotropin secretion induced by GnRH antagonists and the response to GnRH replacement therapy, the following experiment was conducted.

Three long-term ovariectomized cynomolgus monkeys fitted with indwelling jugular vein canulae were utilized for this study. Daily blood samples were drawn under ketamine-induced anesthesia (10 mg/kg, I.M.) for 90 days. On study days 1-6 Antide (3 mg/kg, in propylene/glycol:water, 1:1) was administered via subcutaneous injection. GnRH replacement therapy (5 µg/pulse, 1 pulse/hour given over 1 min, via a Pulsamat infusion pump) was initiated on day 7 and continued for one week, then withheld for one week, then reinitiated for one week in a 7 day on, 7 day off regimen for a total of four exposures.

The results of this experiment are depicted in Figure 1. A clear and profound inhibition of gonadotropin concentrations from pretreatment values of 200-300 ng/ml LH and 100-150 ng/ml FSH to less than 50 ng/ml occurred within 24 hours (LH) and 48 hours FSH of Antide administration. Gonadotropin concentrations remained fully suppressed until the day after initiation of GnRH replacement therapy when they returned to levels approximately characteristic of the ovariectomized animal (greater than 100 ng/ml). Upon cessation of GnRH replacement therapy, gonadotropin concentrations again returned to a fully suppressed condition only to become re-elevated upon reinitiation of GnRH replacement therapy. Each time GnRH replacement therapy was initiated gonadotropin concentrations rose into the normal range, and each time GnRH replacement therapy was withheld gonadotropin concentrations fell to suppressed levels, thus revealing a square wave pattern of gonadotropin secretion synchronized to the delivery of GnRH. Eventual recovery to pretreatment conditions occurred after approximately 80 days,

which is typical for recovery from Antide induced gonadotropin suppression under the six day dose regimen.

This study revealed two important observations: (1) The GnRH antagonist (specifically Antide) maintains its ability to suppress endogenous gonadotropin levels for an extended time interval; and (2) this inhibition of gonadotropin secretion can be overcome with an appropriate GnRH replacement therapy. It follows that gonadotropin levels can be carefully controlled and maintained at a desired level by adjusting the amount and frequency of the GnRH antagonist and GnRH in a manner suitable to achieve that level in the mammal being treated.

Example 2

A second experiment was performed to establish that pulsatile GnRH replacement therapy would induce ovulation in the face of antagonist-induced suppression of endogenous cycles.

Normally cycling cynomolgus monkeys were studied in one of two regimens. Regimen A comprised a series of initial large loading doses of Antide (10 mg/kg, sc), with no further Antide administration. Regimen B comprised an initial 3 mg/kg loading dose followed by 1 mg/kg administered every other day to sustain Antide concentrations at a constant level until ovulation had been successfully induced. In each regimen GnRH replacement was initiated 4 days after the first Antide injection at a rate of 5 μ g/pulse, with one 1 min pulse/hour. The amplitude was subsequently raised to 10 μ g/pulse after approximately 30 days. Daily blood samples were drawn for later determination of estradiol, progesterone and Antide concentrations.

In the monkey treated via regimen A, Antide was administered during the luteal phase as four daily injections of 10 mg/kg. As expected, the concentration of Antide rose rapidly to very high levels (>300 ng/ml) then declined throughout the test period remaining above 15 ng/ml during the

attempted ovulation induction. The initial pulsatile GnRH replacement (5 μ g/pulse) resulted in the elevation of E_2 concentrations to those characteristic of the late follicular phase (>100 pg/ml). However, a pump failure on study day 32 resulted in the loss of that cohort of follicles. When the GnRH pump was restarted, the amplitude of the GnRH pulses was increased to 10 μ g/pulse. This resulted in a rapid and sustained elevation of E_2 concentrations, culminating in ovulation and normal luteal phase P_4 concentrations.

10 In the monkey treated via regimen B, Antide was administered as an initial 3mg/kg bolus followed by 1 mg/kg every other day to achieve a sustained elevation of Antide until ovulation had been successfully achieved. Concentrations of Antide rose promptly to levels between 10 and 20 ng/ml where they remained throughout the course of the study. Once again the initial pulsatile GnRH replacement resulted in elevations of E_2 to those characteristic of the late follicular phase. However, once again therapy had to be discontinued, this time due to a minor infection at the site of needle insertion from the pump. Upon re-initiation of therapy (5 μ g/pulse) E_2 concentrations again rose slowly, but seemed to plateau at 50 to 70 pg/ml for about 10 days. The GnRH pulse amplitude was increased to 10 μ g/pulse on study day 26, which resulted in a rapid rise in E_2 concentrations to normal preovulatory levels, culminating in ovulation with subsequent normal luteal P_4 production. From these studies it is evident that pulsatile GnRH replacement therapy can be used to induce ovulation in mammals which are treated with GnRH antagonists to reduce endogenous gonadotropin levels.

Claims

1. A method of controlling gonadotropin levels in a mammal for a defined treatment period which comprises administering a gonadotropin releasing hormone (GnRH) antagonist in an amount and frequency effective to substantially suppress endogenous gonadotropin levels in said mammal throughout the treatment period and administering gonadotropin releasing hormone (GnRH) in an amount and frequency effective to induce secretion of gonadotropins to maintain a desired level in said mammal throughout the treatment period.
2. A method of inducing ovulation in a mammal which comprises administering a GnRH antagonist in an amount and frequency effective to substantially suppress endogenous gonadotropin levels and administering GnRH in an amount and frequency effective to induce ovulation.
3. A method according to claim 1 or 2 wherein said mammal has polycystic ovarian disease.
4. A method according to claim 1 or 2 wherein said mammal has hyperandrogenism.
5. A method according to claim 1 wherein said mammal has abnormally high levels of luteinizing hormone which are reduced to approximately normal levels as a result of treatment.
6. A method according to claim 1 or 2 wherein said GnRH antagonist comprises a decapeptide of the formula
AA¹-D-pClPhe²-D-3-Pal³-Ser⁴-AA⁵-AA⁶-AA⁷-AA⁸-Pro⁹-D-Ala¹⁰-NH₂ wherein
AA¹ is N-Ac-D-2-Nal, N-Ac-D-pClPhe or N-Ac-D-Cl₂Phe;
AA⁵ is Tyr, acylated Lys, or acylated ACAla;

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AA⁶ is D-acylated Lys or D-acylated ACAla;
AA⁷ is Leu, Aile, Nle, Val, NVal, Abu, or Ala; and
AA⁸ is ILys or IOrn.

7. A method according to claim 6 wherein
5 AA¹ is N-Ac-D-2-Nal
AA⁵ is NicLys, PicLys, MNicLys, MPicLys, INicLys, DMGLys,
or PzCLys; and
AA⁶ is D-NicLys, D-PicLys, D-MNicLys, D-MPicLys, D-INicLys,
D-BzLys, D-PzCLys, D-PzACAla, D-NACAla, D-PACAla.
- 10 8. A method according to claim 6 wherein said GnRH antagonist
is Antide.
9. A method according to claim 1 wherein said GnRH antagonist
is initially administered over a period of one to six days.
10. A method accordingly to claim 1 wherein said GnRH
15 antagonist is administered at approximately regular intervals.
11. A method according to claim 10 wherein said GnRH
antagonist is administered daily, every other day, weekly,
bi-weekly or monthly.
12. A method according to claim 9 wherein said GnRH
20 antagonist is administered approximately monthly.
13. A method according to claim 9 wherein GnRH
administration commences after the first day of GnRH
antagonist administration.
14. A method according to claim 9 wherein GnRH
25 administration commences after completion of GnRH antagonist
administration.
15. A method according to claim 1 or 2 wherein said GnRH is
administered in an episodic or pulsatile manner.

16. A method according to claim 15 wherein said GnRH is administered at about 5 to 10 μ g/pulse at about 60 to 120 minute intervals.

17. A method according to claim 6 wherein said GnRH is administered in a pulsatile manner at about 5 to 10 ug/pulse at about 60 to 120 minute intervals.

18. A method according to claim 17 wherein said GnRH antagonist is Antide.

19. A treatment kit for controlling gonadotropin levels in a mammal which comprises a GnRH antagonist in a dosage form and quantity suitable for administering an amount and frequency effective to substantially suppress endogenous gonadotropin levels in said mammal, and GnRH in a dosage form and quantity suitable for administering an amount and frequency effective to induce secretion of gonadotropins in said mammal to maintain a desired level.

20. A treatment kit for inducing ovulation in a mammal which comprises a GnRH antagonist in a dosage form and quantity suitable for administering an amount and frequency effective to substantially suppress endogenous gonadotropin levels in said mammal, and GnRH in a dosage form and quantity suitable for administering an amount and frequency effective to induce ovulation in said mammal.

21. A treatment kit according to claim 19 or 20 wherein said GnRH antagonist comprises a decapeptide of the formula
AA¹-D-pClPhe²-D-3-Pal³-Ser⁴-AA⁵-AA⁶-AA⁷-AA⁸-Pro⁹-
D-Ala¹⁰-NH₂ wherein
AA¹ is N-Ac-D-2-Nal, N-Ac-D-pClPhe or N-Ac-D-Cl₂Phe;
AA⁵ is Tyr, acylated Lys, or acylated ACAla;

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AA⁶ is D-acylated Lys or D-acylated ACAla;
AA⁷ is Leu, Aile, Nle, Val, NVal, Abu, or Ala; and
AA⁸ is ILys or IOrn.

22. A treatment kit according to claim 21 wherein said GnRH
5 antagonist is Antide.

23. Use of a GnRH antagonist in the manufacture of a
treatment kit according to any one of claims 19 to 22.

24. Use of a GnRH antagonist in the manufacture of a
composition useful for practicing the method according to any
10 one of claims 1 to 18.

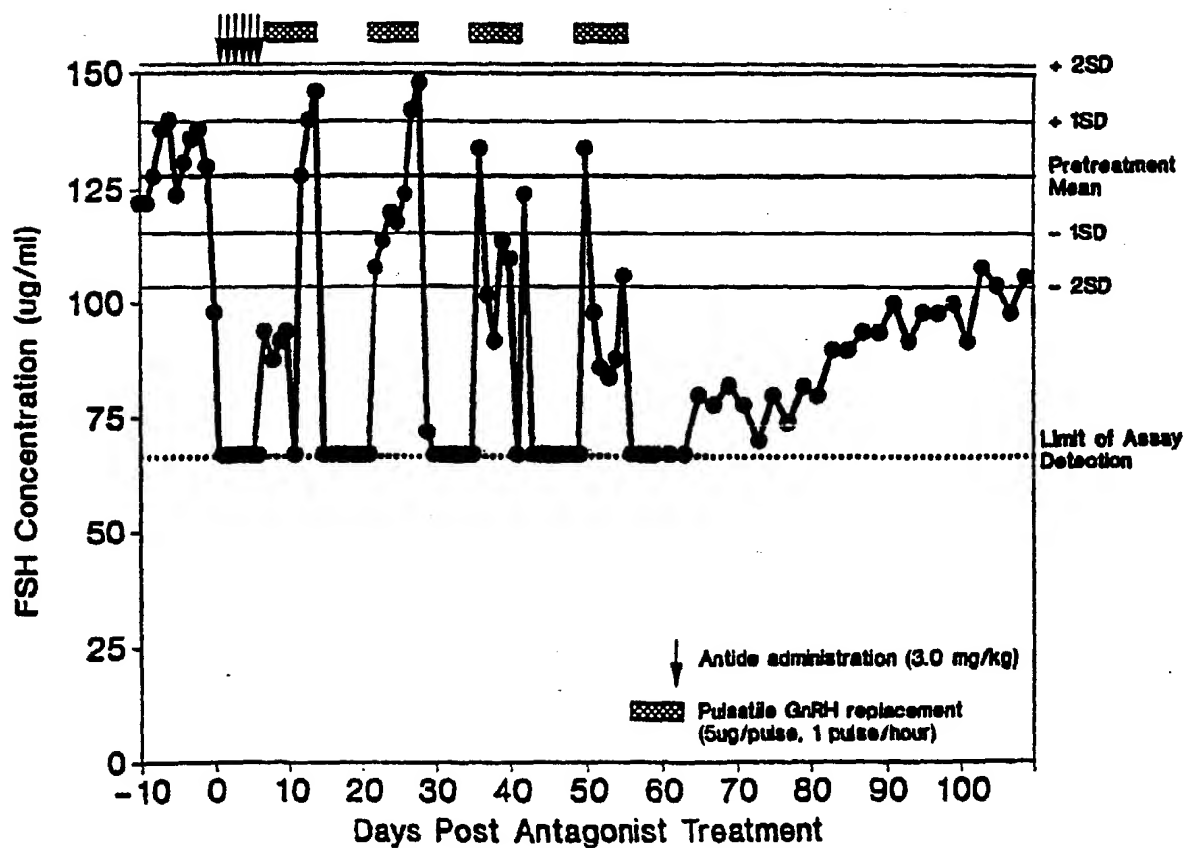
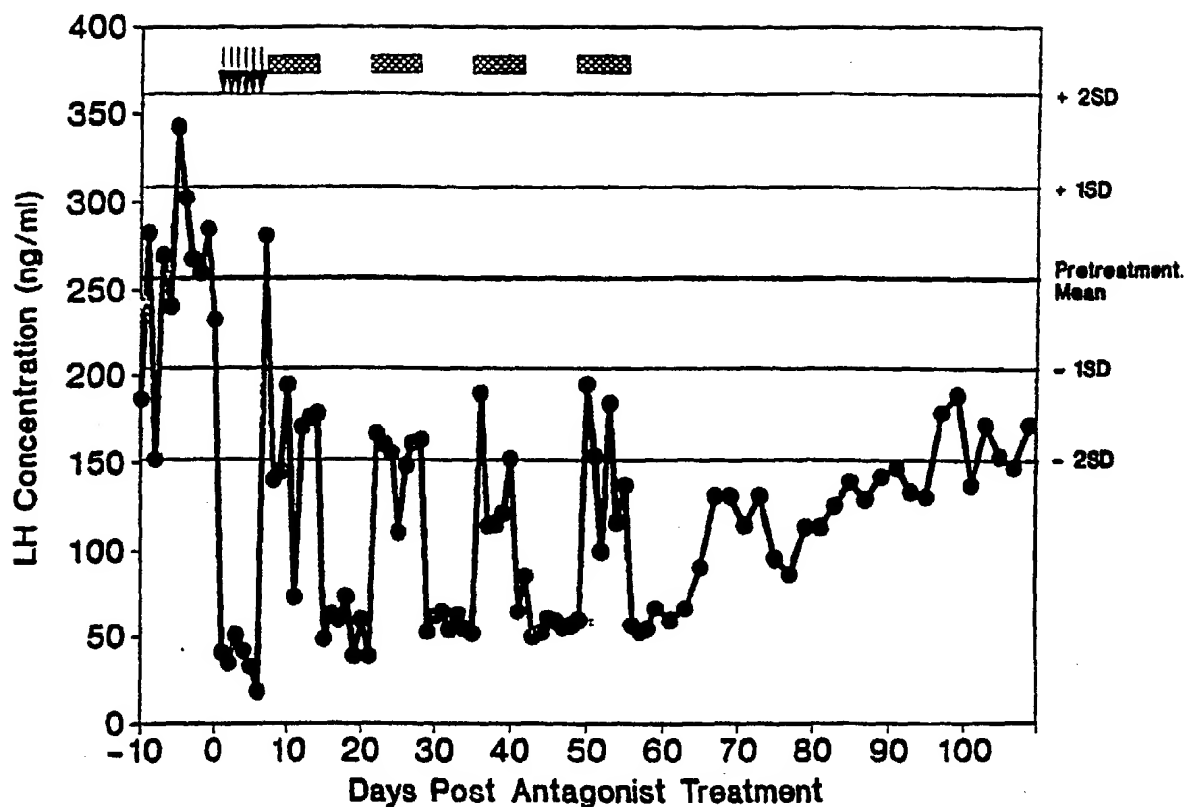


Figure 1



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DK	Denmark				

⁺ It is not yet known for which States of the former Soviet Union any designation of the Soviet Union has effect.

INTERNATIONAL SEARCH REPORT

PCT/US 91/04181

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07K15/00; A61K37/43; //(A61K37/43,37:02)		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X,P	FERTILY AND STERILITY vol. 54, no. 6, December 1990, pages 1140 - 1145; KEITH GORDON ET AL.: 'A novel regimen of gonadotropin-releasing hormone antagonist plus pulsatile GnRh. controlled restoration of gonadotropin secretion and ovulation induction' * Abstract *	1-24
X	EP,A,0 161 063 (HODGEN, GARY D.) 13 November 1985 see abstract & US,A,4 845 077 4 July 1989 cited in the application	1
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
15 JANUARY 1992	23. 01. 92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	LEHERTE C.F.M. 	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9104181
SA 48979

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 15/01/92

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EP-A-0161063	13-11-85	JP-A- 61076421	18-04-86
		US-A- 4845077	04-07-89

US-A-4845077	04-07-89	EP-A, B 0161063	13-11-85
		JP-A- 61076421	18-04-86
